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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,065	12/05/2001	Keith D. Allen	R-648	2751

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EXAMINER
BERTOGLIO, VALERIE E

ART UNIT	PAPER NUMBER
1632	11

DATE MAILED: 01/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,065	ALLEN ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *1-4,11-17 and 35-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-10 and 18-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: *Seq. Compliance Form* .

Election/Restrictions

Applicant's election with traverse of Invention III, claims 9 and 18-33 in paper No. 10, dated 12/02/2002 is acknowledged. Claim 8 was omitted from the restriction and will be examined with Invention III. Applicant's arguments of traversal of the restriction requirement are found partially persuasive and Inventions II and II will be rejoined.

The traversal is partially on the ground(s) that a search of Invention I claims and Invention II or III claims together would not be an undue burden because a reasonable search would produce results related to the targeting construct of Invention I and the cells of Invention II or the animals of Invention III and should thus be rejoined. This argument is not found persuasive because it is maintained that each of the inventions of Invention I and II or Invention I and III require a separate search status on the basis of Inventions II and III require a materially different product from that of Invention I, which is separately classified. In particular, Invention I is directed to methods of making a gene targeting construct that are not necessary to disrupt the glucagon receptor gene in cells or in animals. Materially different constructs can be used to disrupt glucagon receptor gene. Furthermore, the nucleic acid of Invention I and the cells of Invention II or the animals of Invention III, are structurally and functionally different and are patentably distinct. As such, Invention I and Invention II or Invention III require materially different reagents and technical considerations such that a proper search for both inventions would require an extensive search for materially different methods thereby placing an undue search burden upon the Examiner.

With exception of arguments pertaining directly to Inventions II and III, which have been rejoined, the restriction requirement is still deemed proper and is therefore made **FINAL**.

Claims 1-56 are pending, however, claims1-4,11-17, and 35-56 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions, the requirement having been traversed in Paper No. 10. Claims 5-10 and 18-34 are under current examination.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **The sequence in Figure 2A requires a SEQ ID NO**. Applicants must file a "Sequence Listing" accompanied by directions to enter the listing into the specification as an amendment. Applicant also must provide statements regarding sameness and new matter with regards to the CRF and the "Sequence Listing." Applicant is requested to return a copy of the attached Notice to Comply with the reply. Failure to fully comply with the sequence rules in response to the instant office action will be considered non-responsive.

Specification

The disclosure is objected to because of the following informalities:

The statement on page 62, lines 28-30, disclosing that heterozygous mutant mice display decreased fasting glucose levels is contradictory to the statement on page 59, line 12 disclosing that heterozygous mutant mice have increased fasting blood glucose levels. Because Figure 4 supports the statement that heterozygous mutant mice had increased blood glucose levels, this latter statement will be interpreted as the phenotype of the heterozygous mutant mouse.

The word "mutant" is misspelled on page 60, line 5.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-10 and 18-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse or mouse cell whose genome comprises a homozygous disruption in the mouse glucagon receptor gene wherein said mouse exhibits increased tolerance to a glucose challenge, or lower fasting glucose or insulin levels, or increased glucagon levels, or gains less body weight, or exhibits abnormalities in the pancreas or body shape, or exhibits decreased body fat or organ weight, does not reasonably provide enablement for any transgenic non-human animal or a cell of any species with a disruption of any glucagon receptor gene. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 5-7,10 and 34 are directed to a cell comprising a disruption in glucagon receptor gene. Claim 8 is directed to a non-human transgenic animal with a disruption in a glucagon receptor gene. Claims 9 and 18-33 are directed to a transgenic mouse with a disruption in a glucagon receptor gene, wherein the transgenic mouse exhibits high tolerance to glucose challenge (claims 19 and 20), or lower fasting glucose levels (claim 21) or lower fasting insulin levels (claim 22), or increased glucagons levels (claim 23, or gains less body weight (claims 24-26), or exhibits abnormalities of the pancreas (claims 27-31), or exhibits decreased body fat, body weight, organ weight, or abnormal body shape (claim 32), or infertility (claim 33).

The state of the art at the time of filing was such that the phenotype of transgenic knockout mice was unpredictable. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene that were intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph).

The art at the time of filing further held that targeted gene insertion technology was not available for any species other than mouse. Since homologous recombination is required for gene targeting methods, embryonic stem cell technology must be available to carry out the method. Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) teach that non-mouse ES cells capable of providing germline chimeras were not available (page S38, column 1, first paragraph). Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cells lines that contribute to the germ line in any species other than mouse (page 65). Furthermore, other potential methods of generating transgenic embryos using homologous recombination had not been developed at the time the invention was made (McGreath, 2000, Nature, Vol. 405, pages 1066-1069; Kent-First, 2000, Nature Biotechnology, Vol. 18, pages 928-929; Dinnyes, 2002, Cloning and Stem Cells, Vol. 4, pages 81-90). Thus, at the time of filing, the phenotype of transgenic knockout mice was unpredictable and knockout animals could not be prepared for any species other than mouse.

1) The specification does not provide adequate guidance for one of skill in the art to generate non-human transgenic animals having a disruption in the glucagon receptor gene (claim 6) in any species other than mouse. The methods of gene targeting such as employed in the instant invention require embryonic stem cells. The guidance offered in the specification is limited to the production of knockout mice using mouse ES cells and no teachings or guidance are offered in regard to how one would have prepared any other species of animal using targeted mutagenesis. Furthermore, the art at the time of

filing fails to disclose any ES cells other than mouse ES cells that contribute to the germline. Without such guidance, it would require undue experimentation for one of skill in the art at the time of filing to make any transgenic, non-human animal with a disruption in the glucagon receptor gene.

2) Applicants fail to enable the making and/or using a transgenic having a phenotype other than increased tolerance to a glucose challenge, or lower fasting glucose or insulin levels, or increased glucagon levels, or decreased body weight, or exhibits abnormalities in the pancreas or body shape or exhibits decreased body fat or organ weight as encompassed by claims 8,9 and 18. As set forth in the art, the phenotype of a transgenic animal was unpredictable at the time of filing. The specification does not overcome the unpredictability inherent in generating knockout mice such that any phenotype could be obtained other than increased tolerance to a glucose challenge, or lower fasting glucose or insulin levels, or increased glucagon levels, or decreased body weight, or abnormalities in the pancreas or body shape or exhibits decreased body fat or organ weight in glucagon receptor knockout mice. Without such guidance, it would require one of skill in the art at the time the invention was made, undue experimentation to determine how to obtain any phenotype or to use the glucagon receptor knockout mouse having any phenotype other than increased tolerance to a glucose challenge, or lower fasting glucose or insulin levels, or increased glucagon levels, or decreased body weight, or abnormalities in the pancreas or body shape or exhibits decreased body fat or organ weight.

3) The specification teaches that only mice homozygous for a disruption in glucagon receptor displayed increased tolerance to a glucose challenge (page 62, line 30-page 63, lines 1-2), or lower fasting glucose or insulin levels (page 63, lines 9-10), or increased glucagon levels (page 60, lines 4-5and Figure 8), or gains less body weight (page 57, lines 6-8), or exhibits abnormalities in the pancreas(page 56, lines 16-29 and page 57, line 1-5) or body shape or exhibits decreased body fat or organ weight (page 56, lines 9-10), or female infertility (page 61, lines 1-4). The specification did not disclose the claimed phenotypes for mice heterozygous for a glucagon receptor disruption. Therefore, the claims should be limited to a homozygous disruption of the mouse glucagon receptor gene.

4) The specification fails to enable disrupting any glucagon receptor gene in a mouse or any other species or a cell other than a mouse cell. The specification only teaches one mouse glucagon receptor gene (SEQ ID NO: 1; page 10, lines 6-8). The specification does not provide adequate guidance for determining other mouse glucagon receptor genes or that other glucagon receptor genes exist in mouse or have the same function as the glucagon receptor gene disclosed. The specification does disclose a human glucagon receptor gene, however, the specification does not teach knocking out human glucagon receptor gene function in mice or any other animal. Limiting claim 8 to a transgenic mouse, limiting claims 5-7 to a mouse cell and deleting "a" preceding "glucagon receptor gene" in claims 5,8,18,19,21-24,27,32, and 33 would overcome this rejection.

5) The specification fails to enable making a transgenic mouse of either gender with a disruption in the glucagon receptor gene wherein the mouse exhibits infertility (claim 33). The specification discloses that pair wise mating of homozygous mutant mice resulted in one pup (page 61, lines 1-4), which indicated reduced fertility rather than infertility. Furthermore, the homozygous glucagon receptor gene disruption may affect fertility only in a single gender. The specification does not disclose a total lack of fertility and further fails to disclose that the reduced fertility was a result of both reduced male fertility and female fertility as encompassed by claim 33.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "approximately " in claim 26 is a relative term which renders the claim indefinite. The term "approximately" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what the metes and bounds of “an approximately equivalent amount of food” is.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-10, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (*Scientific American*, 1994, vol. 270, pp 34-41) in view of Burcelin (1995, Gene, Vol. 164, pages 305-310) and further in view of Chambers (1996, Nature Genetics, Vol. 12, page 122).

Capecchi taught transforming a cell with a nucleic acid construct comprising a disruption in the HoxA-3 gene, resulting in an inactivating insertion of a selective marker gene into the endogenous HoxA-3 locus, and using said cell to generate a mouse whose genome comprises a disruption in the HoxA-3 gene. Capecchi differs from the claimed invention in that the targeting construct does not disrupt the glucagon receptor gene.

However, at the time the claimed invention was made, Burcelin taught the cloning of the mouse glucagon receptor gene (entire document).

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make cells and a knockout mouse having a disruption in a targeted gene as taught by Capecchi wherein the gene was the glucagon receptor gene as taught by Burcelin. One of ordinary skill in the art would have been sufficiently motivated to replace the Hox3A gene with the glucagon receptor gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by

the generation of a knockout mouse. One of ordinary skill in the art would have been sufficiently motivated to disrupt the glucagon receptor gene to determine its role in hypertension and diabetes as mutations in the human glucagon receptor had been associated with these diseases (Chambers, page 122).

Note that absent any phenotypic requirements for the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention. Capecchi discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning gene and the manifestation of disease (page 41, column 2, 2nd full paragraph).

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio
Patent Examiner

DEBORAH J. REYNOLDS
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Application No.: 10/010065

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: The sequence in Figure 2A requires a SEQ ID NO.

If Necessary, Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE